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Term:

L11 and L12

Display: 10 **Documents in Display Format:** CIT **Starting with Number** 1**Generate:** ☐ Hit List ☒ Hit Count ☐ Side by Side ☐ Image

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Help

Logout

Interrupt

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Edit S Numbers

Preferences

Cases

Search History**DATE:** Wednesday, December 03, 2003 [Printable Copy](#) [Create Case](#)**Set Name Query**
side by side**Hit Count Set Name**
result set*DB=USPT; PLUR=YES; OP=OR*

<u>L13</u>	111 and L12	5221	<u>L13</u>
<u>L12</u>	articular cartilage adj2 osteochondral graft	48447	<u>L12</u>
<u>L11</u>	articular cartilage adj2 regeneration	5240	<u>L11</u>
<u>L10</u>	L7 and articular cartilage	9292	<u>L10</u>
<u>L9</u>	12 same cartilage regeneration same osteochondral graft	48211	<u>L9</u>
<u>L8</u>	12 near cartilage regeneration near osteochondral graft	46120	<u>L8</u>
<u>L7</u>	12 adj1 cartilage regeneration adj1 osteochondral graft	45546	<u>L7</u>
<u>L6</u>	12 adj2 cartilage regeneration adj2 osteochondral graft	45975	<u>L6</u>
<u>L5</u>	12 adj cartilage regeneration adj osteochondral graft	45546	<u>L5</u>
<u>L4</u>	11 and L3	1	<u>L4</u>
<u>L3</u>	growth factor	740616	<u>L3</u>
<u>L2</u>	bone morphogenic protein	182378	<u>L2</u>
<u>L1</u>	5713374.pn.	1	<u>L1</u>

END OF SEARCH HISTORY

WEST**End of Result Set**

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Print

L4: Entry 1 of 1

File: USPT

Feb 3, 1998

DOCUMENT-IDENTIFIER: US 5713374 A

TITLE: Fixation method for the attachment of wound repair materials to cartilage defects

US Patent No. (1):
5713374Detailed Description Text (11):

Defects in articular cartilage can be healed by utilizing a regeneration template formed by combining a porous collagen sponge ("collagen matrix") with a dense collagen membrane as described in our copending application entitled A Multi-staged Collagen-Based Template Or Implant For Use In The Repair of Cartilage Lesions, the entire disclosure of which is incorporated by reference herein. The dense collagen matrix is made with a pore size of less than 1 micrometer, and is cross-linked with a non-cytotoxic agent to increase strength and lengthen resorption time. Because of this dense collagen membrane, the invention can be used in full-thickness defects, including those which traverse the subchondral plate. The dense collagen membrane is placed on the surface of the cartilage defect to prevent cell migration from the subchondral plate and vasculature. The collagen membrane will allow movement and exchange of fluids, nutrients, cytokines and other factors necessary for cartilage regeneration. The thicknesses of the components of the template 12 can vary depending upon the circumstances of use. For example, the thickness of the dense collagen membrane may be in the range of 50 to 200 micrometers or more and the thickness of the porous collagen matrix may be in the range of 0.5 to 8 millimeters or more.

Detailed Description Text (12):

The collagen matrix component of that template has been developed to allow attachment and growth of cells, particularly chondrocytes. In vitro studies have been used to determine the optimal pore size of the porous collagen matrix component of the template. The collagen matrix can be used to immobilize chondrocytes in vitro and support subsequent cell growth. The cell number can then be expanded in vitro, and the collagen matrix can be used to transport the cells to the repair site and retain the cells in position following implantation.

Detailed Description Text (13):

Previous studies have shown that the collagen matrix pore size can be controlled by varying the dispersion pH, collagen concentration and the lyophilization cycle (freezing time, temperature range, and cycle time (Dillion et al. 1986)). The collagen matrices have also been characterized according to their permeability to globular macromolecules. For example, it was found that a pore structure of approximately 15 micrometers would exclude molecules greater than 10.^{sup.6} daltons; a dense collagen membrane had a molecular weight exclusion of 7.times.10.^{sup.4} daltons (Li, 1987). Chondrocytes were grown on type I collagen matrices of varied pore structure in order to determine the effect of the average matrix pore size on cellular growth rate. It was found that the pore structure did not affect the rate of cell growth after 12 days. However, chondrocyte infiltration was greater for average pore sizes greater than 100 micrometers. A parallel study using fibroblasts showed similar cell growth results. It is important to note that the growth rate of fibroblasts on the dense collagen membrane was approximately the same as a porous matrix, but that migration of cells through the membrane was excluded (Pachence et

.al., 1991).

CLAIMS:

2. The method of claim 1 additionally comprising the further step of selecting the cartilage repair template to be a bilayer material for the repair of cartilage defects leading to the regeneration of hyaline-like cartilage, comprising:

a) a first layer comprising a dense collagen membrane having a pore size of less than 1 micrometer which is cross-linked with a non-cytotoxic agent to increase strength and lengthen resorption time, to provide a barrier against movement of cells from the subchondral plate, the membrane being sufficiently permeable to allow the passage therethrough of fluids, nutrients, cytokines, and other endogenous factors necessary for healing; and

b) a second layer secured to the first layer and comprising a porous collagen matrix having a pore size of 50 to 200 micrometers, which permits the ingrowth of cells; and

c) positioning said cartilage repair template in said defect site, such that said dense collagen membrane is located closely adjacent to or in contact with said subshondral plate.

prevents migration, as demonstrated in a canine model of cartilage repair under load-bearing conditions. Preventing migration is important because not only is the tissue regeneration aspect of the implant required at the site, but also because the biomechanics of the joint would not be disrupted by an object that partly or totally obstructs smooth motion of the joint. Another advantage of the invention is that it overcomes the press-fit size limitation of the defect to be treated.

anchors have been used in the past to secure soft tissue to bone, particularly muscle, ligaments, and tendon in and around joints. The anchors are made from biocompatible metals and plastics and are available in a variety of sizes. It was found that suture materials can be secured to the distal aspect of the anchor, prior to placing the anchor into the defect site. A drill hole, is made at the approximate center of the defect. The anchor is then set into the prepared site, allowing the suture lines to freely extend away from the articular surface of the joint.

EXAMPLES OF INVENTION USE

1. Prepare a surgically defined site 4, slightly smaller than the size of the cartilage repair implant or template 12.

2. Drill an appropriately sized hole, (e.g., 1 mm in diameter) approximately in the center of the defect site 4. The hole should be of a sufficient diameter to allow the anchor 11 to be set into place and to permit the passage of a suture 10 therethrough.

3. Attach the appropriate number of sutures 10, e.g., two sutures to an anchor 11 (e.g., product sold as product number Mitek No. 210193 G-II MINI ANCHOR, sold by Mitek Surgical Products, Inc., Norwood, Mass., as also disclosed in U.S. Pat. Nos. 4,898,156 and 4,946,468, the entire disclosures of which are incorporated by reference herein), so that equal sized strands emanate from the distal aspect of the anchor 11, e.g., four. The sutures 10 should be bioresorbable, and should be sized 5-0 or less.

4. Set the anchor 11 into the drill hole, so that the resorbable suture strands 10 protrude from the center of the surgically prepared site, e.g., four (FIG. 2).

5. Pull the suture lines through the cartilage repair implant 12 (FIG. 3).

6. Tie the sutures so that the knot is buried beneath the implant surface or beneath the protective cover, if utilized, and not exposed to the articular surface 1 (FIG. 4).

Defects in articular cartilage can be healed by utilizing a regeneration template formed by combining a porous collagen sponge ("collagen matrix") with a dense collagen membrane as described in our copending application entitled A Multi-staged Collagen-Based Template Or Implant For Use In The Repair of Cartilage Lesions, the entire disclosure of which is incorporated by reference herein. The dense collagen matrix is made with a pore size of less than 1 micrometer, and is cross-linked with a non-cytotoxic agent to increase strength and lengthen resorption time. Because of this dense collagen membrane, the invention can be used in full-thickness defects, including those which traverse the subchondral plate. The dense collagen membrane is placed on the surface of the cartilage defect to prevent cell migration from the subchondral plate and vasculature. The collagen membrane will allow movement and exchange of fluids, nutrients, cytokines and other factors necessary for cartilage regeneration. The thicknesses of the components of the template 12 can vary depending upon the circumstances of use. For example, the thickness of the dense collagen membrane may be in the range of 50 to 200 micrometers or

more and the thickness of the porous collagen matrix may be in the range of 0.5 to 8 millimeters or more.

The collagen matrix component of that template has been developed to allow attachment and growth of cells, particularly chondrocytes. In vitro studies have been used to determine the optimal pore size of the porous collagen matrix component of the template. The collagen matrix can be used to immobilize chondrocytes in vitro and support subsequent cell growth. The cell number can then be expanded in vitro, and the collagen matrix can be used to transport the cells to the repair site and retain the cells in position following implantation.

Previous studies have shown that the collagen matrix pore size can be controlled by varying the dispersion pH, collagen concentration and the lyophilization cycle (freezing time, temperature range, and cycle time (Dillion et al. 1986)). The collagen matrices have also been characterized according to their permeability to globular macromolecules. For example, it was found that a pore structure of approximately 15 micrometers would exclude molecules greater than 10^6 daltons; a dense collagen membrane had a molecular weight exclusion of 7×10^4 daltons (Li, 1987). Chondrocytes were grown on type I collagen matrices of varied pore structure in order to determine the effect of the average matrix pore size on cellular growth rate. It was found that the pore structure did not affect the rate of cell growth after 12 days. However, chondrocyte infiltration was greater for average pore sizes greater than 100 micrometers. A parallel study using fibroblasts showed similar cell growth results. It is important to note that the growth rate of fibroblasts on the dense collagen membrane was approximately the same as a porous matrix, but that migration of cells through the membrane was excluded (Pachence et al., 1991).

The dense collagen membrane can be attached to the collagen matrix prior to cell culture or prior to implantation, using: 1) bioresorbable sutures; or 2) a fusing technique, requiring that the dense collagen membrane be incorporated into the collagen matrix during formation.

It has been shown through a series of in vivo studies that the template with and without the addition of chondrocytes promotes the healing of surgically induced full thickness defects in a rabbit model of cartilage damage. The chondrocyte-seeded templates have been proven, through the use of histologic, biochemical, and mechanical analyses of retrieved implant-tissue sites, to result in repair tissue which appears to be hyaline cartilage. The orientation of the template in the cartilage defect is fundamental to achieve a successful result. The dense layer is placed "downward" into the defect, contacting bone, and the porous layer lies in the place of the natural cartilage. The dense layer has been shown experimentally to inhibit the formation of fibrocartilage.

Without further elaboration the foregoing will so fully illustrate our invention that others may, by applying current or future knowledge, adapt the same for use under various conditions of service.

We claim:

1. An attachment method used to hold a cartilage repair template into a cartilage defect site, the method comprising the steps of:

- (a) anchoring sutures through the subchondral plate into bony tissue, in said defect site, with at least two lines emerging from a surface thereof; and
- (b) using the anchored suture lines to secure the cartilage repair template to the site and wherein the template includes a dense collagen membrane which is positioned closely adjacent to or against said subchondral plate.

5

2. The method of claim 1 additionally comprising the further step of selecting the cartilage repair template to be a bilayer material for the repair of cartilage defects leading to the regeneration of hyaline-like cartilage, comprising:

- a) a first layer comprising a dense collagen membrane having a pore size of less than 1 micrometer which is cross-linked with a non-cytotoxic agent to increase strength and lengthen resorption time, to provide a barrier against movement of cells from the subchondral plate, the membrane being sufficiently permeable to allow the passage therethrough of fluids, nutrients, cytokines, and other endogenous factors necessary for healing; and
- b) a second layer secured to the first layer and comprising a porous collagen matrix having a pore size of 50 to 200 micrometers, which permits the ingrowth of cells; and
- c) positioning said cartilage repair template in said defect site, such that said dense collagen membrane is located closely adjacent to or in contact with said subchondral plate.

3. The method of claim 2 additionally comprising the step of selecting the template to comprise autologous periosteum placed on top of the collagen matrix and the matrix is initially devoid of cells.

4. The method of claim 2 additionally comprising the step of selecting the template to comprise a collagen film placed on top of the collagen matrix and the matrix is initially devoid of cells.

6

5. The method of claim 2 additionally comprising the step of selecting the template to comprise chondrocyte cells cultured ex vivo with the porous collagen matrix so that the chondrocytes permeate the collagen matrix.

6. The method of claim 2 additionally comprising the step of selecting the template to comprise a piece of autologous periosteum placed on top of the collagen matrix containing the chondrocyte cells.

7. The method of claim 2 additionally comprising the step of selecting the template to comprise a collagen film placed on top of the collagen matrix containing the chondrocyte cells.

8. The method of claim 2 additionally comprising the step of attaching the dense collagen membrane to the collagen matrix using a resorbable suture.

9. The method of claim 2 additionally comprising the step of applying the dense collagen membrane to the collagen matrix during formation of the bilayer material.

10. The method of claim 2 additionally comprising the step of selecting the dense collagen membrane to have a thickness in the range of 50 to 200 micrometers.

11. The method of claim 2 additionally comprising the step of selecting the porous collagen matrix to have a thickness in the range of 0.5 to 8 millimeters.

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